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Investigating the pathways in primary practice leading to the diagnosis of central hypothyroidism

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Abstract

Aim Clinical diagnosis of central hypothyroidism is not always obvious: patients may live for years with symptoms. Endocrinologists and biochemists have suggested that a first-line TSH strategy will lead to avoidable delays in diagnosis and treatment of patients with central hypothyroidism. In order to improve timely diagnosis, and thus decrease morbidity from a treatable disease, this study aimed to investigate the diagnostic journey of patients with central hypothyroidism in the Waikato region of New Zealand.

Method A retrospective convenience sample seeking note review and semi-structured interviews were carried out with 16 patients who had a diagnosis of central hypothyroidism that was not caused by pituitary surgery or radiotherapy to the pituitary or hypothalamus.

Results Seventy-five percent of participants had tests performed in general practice with results suggesting either pituitary disease or that further investigation would be required. In 38% (6/16) of participants diagnosis was made by the general practitioner. Time to diagnosis ranged from 3 months to more than 12 months. Seven participants identified having 3–6 visits to their general practitioner and five participants made 6 to 12 visits to their general practitioner prior to diagnosis. Lethargy was the most common symptom in 94% of participants. This was followed by changes in skin texture and body hair distribution and texture in 75% of participants and headaches in 63% of participants.

Conclusion Due to the era during which these patients were diagnosed, we did not find that a delay in diagnosis was due to an absence of FT_4 requests; which a first-line TSH strategy would imply. It is important to recognise that a normal TSH does not exclude central hypothyroidism. By raising awareness with general practitioners of pituitary disease, with potential for deficiency of other anterior pituitary hormones, would focus more specific questioning on related symptoms.

Central hypothyroidism is rare and is associated with a varied and prolonged course of somewhat vague symptoms. Since October 2005, recommendations have been made to limit thyroid function testing to the use of thyroid stimulating hormone (TSH) as a first-line strategy for investigating thyroid function.[1] This has been developed in response to economic pressures to reduce the overwhelming number of requests for tests.[2-4]

The majority of thyroid function testing in adults are within the normal range,[5] which supports the view that thyroid tests are requested in the absence of strong clinical suspicion of disease.[6] Recommendations, therefore, would appear appropriate.

However, a normal TSH does not exclude central hypothyroidism and endocrinologists and biochemical pathologists have suggested that a TSH first-line strategy will lead to avoidable delays in diagnosis and treatment for patients with this condition.[2,3,6]

Central hypothyroidism, formerly known as secondary hypothyroidism, relates to anatomical or functional conditions of the pituitary or hypothalamus, or both.[7] The term conveys quantitative and qualitative abnormalities of TSH secretion, irrespective of whether it is of hypothalamic or pituitary origin.[7] Central hypothyroidism is rarely an isolated defect, usually part of a more complex condition, hypopituitarism, which also affects other pituitary hormone secretions such as growth hormone, gonadotropin, prolactin and adrenocorticotropin hormone.[7]

Current literature suggests that the incidence of hypopituitarism which includes central hypothyroidism is around 4-5 per 100,000 population per year.[2,7,8] It is distributed equally between sexes and peaks between 30 and 60 years of age.[7]

The causes of central hypothyroidism vary, with the most common cause being pituitary adenomas, which account for over 50% of cases (see Table 1).[7]

Table 1. Causes of acquired central hypothyroidism

Cause
Classical causes
Space-occupying lesions (pituitary adenoma, craniopharygioma, etc)
Radiation to the pituitary/hypothalamus
Vascular disease (Sheehan syndrome, etc)
Non-classical causes
Traumatic brain injury or subarachnoid haemorrhage
Infection
Inflammation (lymphocytic hypophysitis)
Idiopathic

Modified from Yamada, 2008 [9]

The clinical presentation of central hypothyroidism can often be similar to that of primary thyroid disease.[7,10,11] The investigations into the diagnosis of central hypothyroidism are hampered by the use of TSH alone as a first-line thyroid test.[12]

Current recommendations for investigating thyroid function are believed to be a barrier for general practitioners in diagnosing central hypothyroidism and may lead to under- or delayed diagnosis and treatment;[3] further potentially increasing morbidity and reducing the quality of life for these patients.[2,6]

Best Practice Advocacy Centre (BPACnz) guidelines suggest a first-line TSH policy based on symptomatic presentation – showing that unless the patient has a goitre or delayed reflexes in which hypothyroidism is suspected– the likelihood of thyroid dysfunction is low (below 3%).[13] It is acknowledged that there are limitations in using this strategy when investigating central hypothyroidism.[1]

The majority of thyroid function tests are requested by primary care doctors who may have very little experience with pituitary disease and may not consider that a patient with symptoms but a normal TSH value may have central hypothyroidism.[3,6,14]

In order to improve timely diagnosis and thus decrease morbidity from a treatable disease, this study aimed to investigate the diagnostic journey of patients with central hypothyroidism in the Waikato region.

Research design and methods

We used note review and semi-structured questionnaires to retrospectively review patients with a diagnosis of central hypothyroidism; following ethics approval from the Northern Y Regional Ethics Committee (NTY/08/09/091).

We sought a convenience sample of 20 patients from the 100 patients with a diagnosis of hypopituitarism (including those with panhypopituitarism and central hypothyroidism) whose details were held on the Waikato Hospital endocrine database.

Inclusion criteria were patients with confirmed central hypothyroidism as evidenced by patterns of thyroid function testing and consultant diagnosis from the Waikato endocrine database and patients with a diagnosis of central hypothyroidism who presented to the endocrinology department for a routine visit while the study was being carried out.

Exclusion criteria were patients who were diagnosed with central hypothyroidism before 1990 to reduce recall bias and patients whose diagnosis was as a result of pituitary surgery or radiotherapy to the pituitary or hypothalamus. The pathway for surgical patients is through secondary care and is outside the aims of this study.

A timeline of the diagnostic process was constructed for each patient as accurately as possible from the hospital files. Further information was supplemented through patient interviews.

The semi-structure questionnaires were conducted either face-to-face at the patient's home or over the telephone depending on the patient's place of residence (e.g. if >1 hour's drive from Waikato Hospital). General questions for every participant included information about the symptoms leading to general practitioner visits and to their first endocrinology visit leading to diagnosis. These were supplemented with specific questions about the experience leading up to their diagnosis to attain a full picture of the process.

With the patients' permission, their general practitioner and specialists who were involved with their care around the time of diagnosis, including those from outside of Waikato, were contacted for further information if needed.

This study was part of a 10-week summer studentship carried out over the summer of 2008/09 as part of a larger body of work on hypothyroidism in general practice.[15]

Due to the time limitation of the study, a convenience sample was undertaken based on the first 20 people who met the criteria from the order in which they appeared in the database (by NHI number) or referred by the endocrinology team. While we set a minimum diagnosis date after 1990, those with an NHI number (a 3-letter, 4-number

health identifier) who are early in the numbering sequence, e.g. closer to AAA1111, are likely to be older.

We aimed to include 20 participants for detailed assessment, a number considered large enough yet manageable within the time constraints of the study.

Results

Of the 20 people selected, 16 agreed to take part in the study. Eight were male and 8 were female, ages ranged from 39–83 years (mean age 65, median age 67.5). The age range at diagnosis was 35-80 years (mean age 58, median age 57.5). Our sample included one Māori and 15 New Zealand European participants.

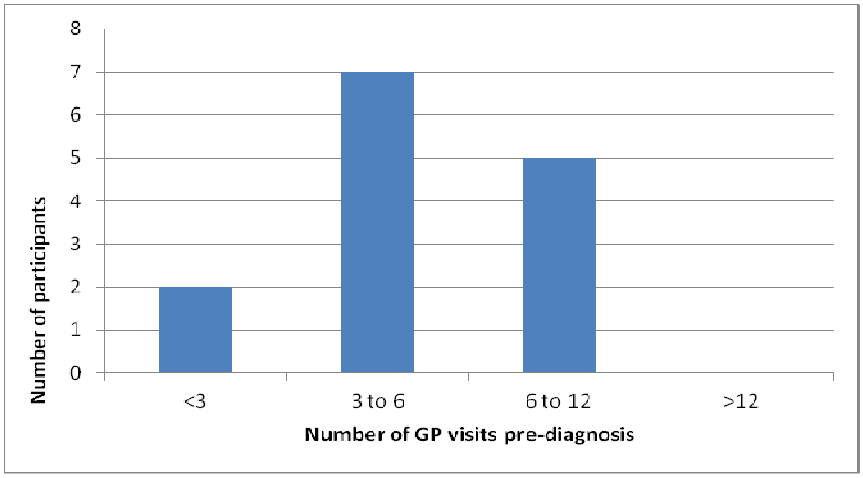
Testing thyroid function—Both TSH and T_4 tests were taken in 81% (13/16) participants prior to their first endocrine assessment, with 75% (12/16) having results suggesting either pituitary disease or that further investigation would be required. Of the 13 participants with prior testing, general practitioners requested 69% (9/13) of these.

In 38% (6/16) of participants diagnosis was made by the general practitioner. For two participants, their diagnosis was made when, independently of each other, they had moved to register with the same general practitioner. Another two participants had their diagnosis immediately identified by their general practitioner and in the remainder, a further two participants, central hypothyroidism was identified by their general practitioner after a period of more than six months.

For five participants (31%) a diagnosis of primary hypothyroidism had been made by the general practitioner prior to their correct central hypothyroidism diagnosis.

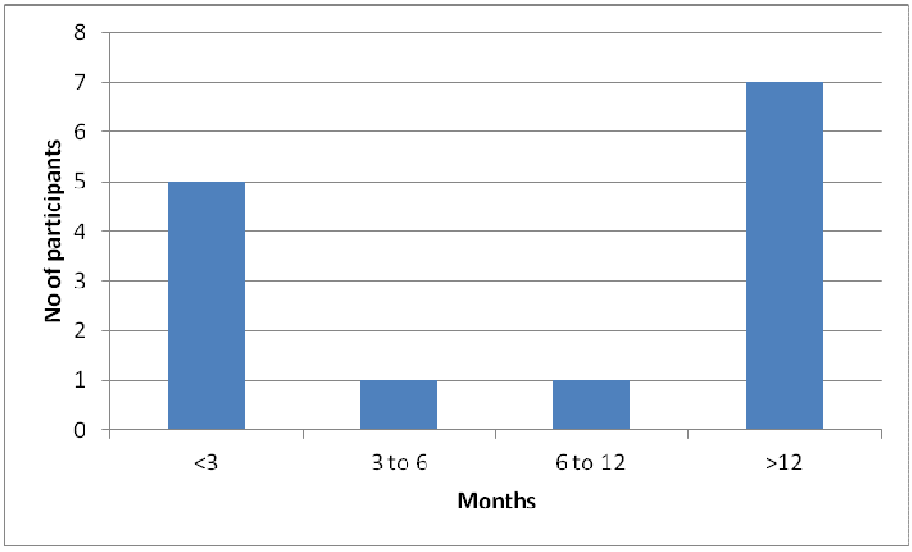
Length of diagnostic process—Time to diagnosis ranged from 3 months to more than 12 months. Seven participants identified having 3–6 visits to their general practitioner and five participants made 6–12 visits to their general practitioner prior to diagnosis. (Figure 1).

Figure 1. Number of GP visits pre-diagnosis



Symptoms—One or more of the following symptoms were reported by the participants: headaches, lethargy, visual disturbances, weight change, joint or muscle pain, change in skin texture, change in body hair distribution or texture, mood changes, irritability, menstruation irregularities in women, loss of facial hair in men, erectile dysfunction and loss of sexual drive. Five participants had symptoms for less than three months, while seven participants had symptoms for greater than a year before seeing a general practitioner. Thirty-eight percent (6/16) of participants lived with symptoms for more than 2 years (Figure 2).

Figure 2: Duration of symptoms pre-diagnosis



Lethargy was the most common symptom in 15/16 participants. This was followed by changes in skin texture and body hair distribution and texture (12/16), and headaches (10/16). Of the 16 participants, nine were diagnosed upon acute admission to Waikato Hospital with symptoms severe enough to cause in-patient admission.

Discussion

Central hypothyroidism is rare: the incidence of central hypothyroidism is approximately 0.005% in the general population.[7] The rarity of central hypothyroidism means the likelihood of having this condition is small, however, there is a suggestion that it may be more common than is reported.[2] Symptoms are vague and there is low clinical suspicion for this condition.[14] However, missing central hypothyroidism is potentially life-threatening as there may be coexistent ACTH/cortisol deficiency which could ultimately be fatal if missed.

Thyroid function test results are often used by general practitioners as a diagnostic tool.[5] Because central hypothyroidism is rare, we identified known cases in order to

examine the journey of the participants to diagnosis. Three methods of information gathering were used to ensure accuracy of information; using each source to confirm or correct another.

Eighty-one percent (13/16) of participants had at least one abnormal thyroid function test result prior to being seen by an endocrine specialist. The majority of participants in this study were diagnosed prior to October 2005 when current BPACnz guidelines for investigating thyroid function were released. The use of TSH, FT_4 and FT_3 by general practitioners were not limited at this time.

Of participants who received thyroid function tests prior to their first endocrine specialist appointment, 12 had results that warranted further investigation. Contrary to what has been currently stated in the literature, that a first-line TSH policy will delay diagnosis,[2,3] even with the full range of thyroid function tests, general practitioners were failing to investigate abnormal results.

Clinical suspicion of central hypothyroidism needs to be raised. Earlier identification of central hypothyroidism would avoid patients reaching a point where immediate action is required. Greater provision for reflective testing which implies additional testing at the discretion of the reporting biochemical pathologist given relevant clinical and biochemical information would provide timely input into the diagnostic process.[14] This is in contrast to reflex testing, where additional tests are added automatically.[1,14]

Several prevalent symptoms of central hypothyroidism are like those of primary hypothyroidism;[7 14] causing difficulties in diagnosis. Thirty-one percent of participants (5/16) were misdiagnosed with primary hypothyroidism. When presented with vague symptoms of thyroid dysfunction, investigating central hypothyroid-specific symptoms associated with other hyposecretion of other pituitary hormones may help such as secondary amenorrhea, erectile dysfunction, nausea and anorexia.

Changes in skin texture and body hair distribution may be evident–the skin is pale and cool in central hypothyroidism compared with coarse and dry from primary hypothyroidism; loss of body hair and thinning of lateral eyebrows are usually more pronounced in central hypothyroidism. Body weight is likely to be reduced rather than increased in central hypothyroidism.[7] In addition, periorbital and peripheral oedema and hoarseness of the voice are uncommon in central hypothyroidism.

The small number of participants interviewed is a limitation of this study, although it can be argued that the message they gave about their symptoms was consistent. Due to participants' age or the length of time since diagnosis, this study is likely to have some recall bias. However the three methods used–hospital records, patient interview and general practice records were able to clarify where there may have been gaps.

Conclusion

A first-line TSH strategy works only if the hypothalamic-pituitary-axis is normal.[9] This strategy may also work as long as limitations are appreciated.[16] While it can be argued that symptoms such as tiredness and lethargy are common in the general population, these findings are also common in patients with a diagnosis of central hypothyroidism. The diagnosis of central hypothyroidism in the Waikato area was delayed for the majority of participants until they had received specialist involvement due to a lack of recognition by general practitioners.[2,14,17,18] Due to the era during

which participants were diagnosed, i.e. no recommendations for restriction on thyroid function testing, we did not find that a delay in diagnosis was due to an absence of FT_4 requests which a first-line TSH strategy would imply.

Raising awareness with general practitioners of pituitary disease with potential for deficiency of other anterior pituitary hormones would focus more specific questioning on related symptoms. Missing the diagnosis of central hypothyroidism could miss or delay the opportunity to diagnose a significant pituitary tumour with potential for visual loss.

Central hypothyroidism is rare, but if general practitioners suspect abnormalities in thyroid function, it is essential that they accurately interpret thyroid function tests, seek advice from endocrinologists and biochemical pathologists, recognise that TSH may be unreliable, and thoroughly pursue relevant symptoms.

Bullet point summary

- Clinical diagnosis of central hypothyroidism is not always obvious
- A normal TSH does not always equate with normal thyroid function
- Central hypothyroidism is rare at around 4-5 cases per 100,000 population per year
- Enquiring about symptoms related to other pituitary hormone deficiencies may be helpful.

Competing interests: None known .

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